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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,788	07/03/2003	George B. McDonald	8105-009-US-CON	6992

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CATALYST LAW GROUP, APC
9710 SCRANTON ROAD, SUITE S-170
SAN DIEGO, CA 92121

EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

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11/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,788	MCDONALD, GEORGE B.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 10/22/07

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted October 22, 2007 wherein claim 1 is amended. This application is a continuation of 09/753814, now abandoned, filed January 3, 2001, which claims benefit of provisional application 60/233194, filed September 15, 2000.

Claims 1-18 are pending in this application.

Claims 1-18 as amended are examined on the merits herein.

Applicant's amendment, submitted September 22, 2007, with respect to the rejection of instant claims 1-18 under the doctrine of obviousness-type double patenting for claiming the same invention as claims 1-40 of US patent 6096731, has been fully considered and found to be persuasive to remove the rejection as claims 1-40 of 6096731 do not encompass a method wherein treatment with a topically active corticosteroid is started at least 29 days post transplantation. Therefore the rejection is withdrawn.

The following rejections of record in the previous office action are maintained:

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et al. (Reference of record in previous office action) in view of Bertz et al. (Reference of record in previous office action)

McDonald et al. teaches that oral administration of the particular topically active corticosteroid, beclomethasone dipropionate (BDP), **alone** in the form of a capsule or **in combination with prednisone** (in the language of instant claim 16) is useful in a method of treating graft-versus-host disease in a human following organ allograft transplantation or stem cell transplantation for 30 days (see abstract and page 28, 1st paragraph, right column). McDonald et al. also teaches that the subject has damaged tissue in the intestinal mucosa and liver, in the language of claims 3, 4, and 6 (p. 32, table 4). McDonald et. al. also teaches the effective amount of beclomethasone dipropionate to be administered as 8 mg per day (p. 29, left column, under the heading *Formulation of BDP and Placebo Capsules*), within the range of 4-12 mg/day set by the instant claim 2. McDonald et. al. also discloses that the capsules administered were either uncoated (to dissolve in the stomach) or enteric-coated (to dissolve in the intestine) in the language of instant claim 10(p. 29, left column, under the heading *Formulation of BDP and Placebo Capsules*). McDonald discloses that the treatment was well-tolerated, and that typical side effects of corticosteroids, such as microbial infections, hypercortisolism, and adrenal insufficiency, were not observed during the treatment. (p. 32, left column, first paragraph, under the heading, "Toxicity from Treatment," and p. 33, left column, last paragraph – right column, first paragraph)

McDonald et. al. also reveal the aim for the study therein to compare the effectiveness of oral BDP to that of placebo capsules in the claimed method herein, and also to examine the frequency of infection in patients treated with beclomethasone dipropionate. See abstract and the entire article, especially p. 29, left column, first paragraph and right column, 3rd paragraph. McDonald et al. does not expressly disclose the long-term therapy (i.e., 29-56 days) in the claimed method, or therapy wherein administration of the topically active corticosteroid commences at least 29 days post-transplantation.

Bertz et al. discloses a method of treating graft-versus-host disease by administering oral budesonide as a topically active corticosteroid. (p. 1186, left column, second paragraph - right column, third paragraph) At enrollment, patients had a mean time of 30 days since transplantation, with actual times ranging between 10 and 310 days. (p. 1186, left column table 1) The duration of the therapy was between 6-70 days, varying from patient to patient, with no side effects observed in any patient. (p. 1187, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP or Budesonide alone or with prednisone over the long term (i.e. 29-56 days) starting at least 29 days post-transplantation. One having ordinary skill in the art at the time of the invention would have been motivated to orally administer BDP or Budesonide alone or with prednisone in the long term (i.e. 29-56 days) since the administration of BDP alone or with prednisone for 30 days or les is known according to the prior art, and a subject may not have fully recovered from their

condition after 30 days, and further because Bertz et al. discloses that budesonide can also be administered for the treatment of graft-versus-host disease. Thus, one of ordinary skill in the art would reasonably extend the therapy to the longer period from 30 days or less to 56 days if such treatment is still required after 30 days from the beginning of treatment. One of ordinary skill in the art would reasonably have expected success in administering the therapy for more than 30 days because McDonald discloses that no side effects were noticed in patients administered beclomethasone dipropionate, and furthermore because Bertz et al. discloses that patients maintained on a similar topically active corticosteroid, budesonide, showed no side effects when maintained on the drug for up to 70 days. In view of these disclosures, one of ordinary skill in the art would have determined that beclomethasone dipropionate or budesonide could reasonably be administered for a duration of over 30 days due to the observed lack of side effects for topically active corticosteroids. Moreover, determination of the time period of administration is considered well within the skill of the artisan, involving merely routine skill in the art.

Furthermore, it would have been obvious to begin the therapy at least 29 days post-transplantation (for example in patients who are discontinuing prednisone therapy) because many of the patients studied by Bertz et al. are begun on topically active corticosteroid therapy at more than 29 days, in some cases as long as 310 days after transplantation. One of ordinary skill in the art would reasonably have interpreted these results to indicate that patients 29 or more days post-transplantation can be started on topically active corticosteroid therapy with a reasonably expectation of success.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument:

Applicant's arguments and amendment submitted October 22, 2007 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection.

Applicant argues that the most recent amendment obviates the cited references. However, as discussed above, Bertz et al. already clearly suggests starting topically active corticosteroid at a time of 29 or more days post transplantation, as indicated by the day post-transplant range cited in the description of the patient population. Therefore the claims as amended are still obvious over the cited prior art.

Thus Applicant's arguments are not found to be convincing and the rejection is maintained and made **FINAL**.

Claims 1-10 and 12-18 are rejected under 35 USC 103(a) as being unpatentable over Baehr et. al. (Reference of record in previous office action) in view of Bertz et al. (Reference included with PTO-892)

Baehr et. al. teaches that oral administration of the particular topically active corticosteroid, beclomethasone dipropionate, alone in the form of a capsule for 28 days, is a useful method of treating graft-versus-host disease in a human following organ allograft transplantation of human leukocyte antigen mismatched marrow. (p. 1233, right column, under the heading, *clinical efficacy*) Patients entered the study at a mean period of 58 days post-transplantation. (p. 1233, left column, last paragraph) Baehr et.

al. also teaches that, in subjects already taking prednisone, "The prednisone dose at study entry was maintained throughout the study whenever medically possible," (p. 1232. left column, 3rd paragraph) meaning that BDP was administered in conjunction with another prophylactic agent as taught by instant claim 16. Baehr et. al. also teach the use of BDP in subjects who have tissue damage of the intestinal mucosa and liver. Baehr et. al. also teaches the effective amount of beclomethasone dipropionate to be 8 capsules of 1 mg each per day, for a total dose of 8 mg per day, in accordance with instant claim 2. (p. 1232, under the heading, *formulation and dosing of beclomethasone dipropionate*) Although adrenal axis function was reduced in patents receiving BDP, no clinical side effects were observed. (p. 1234, right column, p. 1236, right column, second paragraph) Baehr et. al. also suggest that the purpose of the study is to evaluate whether the oral BDP is a safe effective treatment for the instant disease. See the abstract of Baehr et. al. Baehr et. al. does not explicitly disclose the long-term therapy (i.e. 29-56 days) of the claimed invention.

Bertz et al. discloses a method of treating graft-versus-host disease by administering oral budesonide as a topically active corticosteroid. (p. 1186, left column, second paragraph - right column, third paragraph) At enrollment, patients had a mean time of 30 days since transplantation, with actual times ranging between 10 and 310 days. (p. 1186, left column table 1) The duration of the therapy was between 6-70 days, varying from patient to patient, with no side effects observed in any patient. (p. 1187, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP or Budesonide alone or with prednisone over the long term (i.e. 29-56 days), beginning at least 29 days after transplantation.

One having ordinary skill in the art at the time of the invention would have been motivated to orally administer BDP or budesonide alone or with prednisone in the long term (i.e. 29-56 days) since the administration of BDP alone or with prednisone for 30 days or les is known according to the prior art, and a subject may not have fully recovered from their condition after 30 days, and further because Bertz et al. discloses that budesonide can also be administered for the treatment of graft-versus-host disease. Thus, one of ordinary skill in the art would reasonably extend the therapy to the longer period from 30 days or less to 56 days if such treatment is still required after 30 days from the beginning of treatment. Furthermore because Bertz et al. discloses that patients maintained on a similar topically active corticosteroid, budesonide, showed no side effects when maintained on the drug for up to 70 days. In view of these disclosures, one of ordinary skill in the art would have determined that beclomethasone dipropionate or budesonide could reasonably be administered for a duration of over 30 days due to the observed lack of side effects for topically active corticosteroids. Moreover, determination of the time period of administration is considered well within the skill of the artisan, involving merely routine skill in the art.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument:

Applicant's arguments and amendment submitted October 22, 2007 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection.

Applicant argues that the most recent amendment obviates the cited references, specifically by requiring that therapy commence at least 29 days post-transplantation. However, as discussed above, Baehr et al. describes a therapy administered to patients who were a mean period of 58 days post-transplantation, ranging from 21 up to 231 days. Bertz et al. also clearly suggests starting topically active corticosteroid at a time of 29 or more days post transplantation, as indicated by the day post-transplant range cited in the description of the patient population. In view of the teaching of both cited references, one of ordinary skill in the art would clearly have been motivated to administer the therapy to patients 29 or more days post-transplantation, for example those discontinuing prednisone therapy, and would have reasonably expected success in doing so because of the success of Baehr et al. and Bertz et al. in treating similar patients. Therefore the claims as amended are still obvious over the cited prior art.

Thus Applicant's arguments are not found to be convincing and the rejection is maintained and made **FINAL**.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et. al. (References of record in previous office action) or alternately Baehr et. al. (References of record in previous office action), in view of Bertz et al. (Reference included with PTO-892) in view of, alternately, US patents Lundquist, Brancq et. al., or

Benita et. al. (US patents 5843465, 5958431, and 6007826, References of record in previous office action).

The disclosures of McDonald et. al. and Baehr et. al. in view of Bertz et al. is discussed above. The above references do not disclose a method in which the active agent is administered as a pharmaceutical emulsion.

Lundquist, Brancq et. al., and Benita et. al. all disclose pharmaceutical emulsions, and methods for preparing the same from hydrophobic pharmaceutical compounds. (see, for example, claim 1 of Lundquist, claim 1 of Brancq et. al., or claim 1 of Benita et. al.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to orally administer BDP alone or with prednisone as an emulsion, in the manner of claim 11, as disclosed by the aforementioned US patents.

One having ordinary skill in the art at the time of the invention would have been motivated to administer the compound as an emulsion to increase solubility and bioavailability. One of ordinary skill in the art would have reasonably expected success because determination of the optimal dosage formulation is considered well within the skill of the artisan, involving merely routine skill in the art.

Thus the invention as a whole is *prima facie* obvious over the prior art.

Response to Argument:

Applicant's arguments and declaration submitted March 23, 2007 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection. The reasons are the same as those discussed above

concerning McDonald et al. and Baehr et al. Thus Applicant's arguments are not found to be convincing and the rejection is maintained and made **FINAL**.

Claims 1, 2, 4, 5, 9, 10, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Punch et. al. (Of record in previous office action), in view of Sequeira et. al. (US patent 6057307, of record in previous office action)

Punch et. al. teaches that systemically administered corticosteroids are a standard therapy used to reduce the likelihood of rejection in liver transplant recipients, a therapy which is complicated by the presence of multiple side effects including weight gain, hypertension, hyperlipidemia, glucose intolerance, hirsutism, acne, and osteoporosis. (p. 783, first paragraph) The object of the research disclosed by Punch et. al. was an attempt to relieve said side effects by withdrawing corticosteroid treatment 1 year after transplantation. It should be noted that this reference indicates that corticosteroids can be administered for up to a year in the case of liver transplant recipients, which is well beyond the 30-day point defined by Applicant as marking long-term therapy. Punch et al. does not disclose topical administration of corticosteroids in order to treat host-versus-graft disease of the liver with reduced side effects. Punch et al. also does not disclose a method wherein therapy with a topically active corticosteroid is begun at least 29 days after transplantation.

Sequeira et. al. teaches, "A method of treating a corticosteroid-responsive disease of the lower airway passages or lungs, which comprises administering as initial or maintenance therapy to the surfaces of said lower airway passages or lungs, at least

once daily, a substantially non-systemically bioavailable amount of aerosolized particles of mometasone furoate effective for treating said disease." (Claim 1) In other words, the invention of Sequeira et. al. comprises a method of locally treating a disease responsive to corticosteroids by administering mometasone furoate in an inhaleable form locally to the lungs. Sequeira et. al. also teaches that systemically bioavailable corticosteroids cause unwanted side effects (column 1, lines 51-55), and that a major benefit of the claimed invention is that mometasone furoate avoids this complication because it does not become systemically bioavailable from the gastrointestinal tract. (Column 3, lines 40-54) Although Sequeira et. al. does not mention host-versus-graft disease due to lung transplantation by name, this condition falls within the claim language of, "a disease responsive to corticosteroids," which would be treatable by, "a substantially non-systemically bioavailable amount of aerosolized particles of mometasone furoate effective for treating said disease."

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teaching of Punch et. al. by administering an orally available, topically active corticosteroid such as mometasone furoate to the liver, in place of or in addition to standard systemic corticosteroid therapy, by oral administration to a patient suffering from either graft-versus-host or host-versus-graft disease affecting the intestine and/or liver.

One of ordinary skill in the art would have been motivated to modify the invention in this way in order to treat liver transplant rejection without causing the severe systemic side effects which are observed with existing corticosteroid therapy.

One of ordinary skill in the art would have reasonably expected success because, as taught by Punch et. al. existing corticosteroids were therapeutically effective against liver transplant rejection to the point that they were in common use despite their substantial side effects, and because mometasone furoate was already known, by Sequeira et. al., to be effective at treating corticosteroid-responsive diseases.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to start treatment with a topically active corticosteroid such as mometasone furoate at a time of 29 days or later after transplantation. One of ordinary skill in the art would have been motivated to begin administration of the topically active corticosteroid to a patient who was receiving therapy with systemically active corticosteroids such as prednisone, at later than 29 days post-transplant, in order to substitute the safer, better tolerated topically acting corticosteroid for the previous systemically active corticosteroid. One of ordinary skill in the art would reasonably have expected success because the prior art already discloses that topically active corticosteroids can be used to locally treat corticosteroid-responsive diseases, such as transplant rejection.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments and declaration submitted March 23, 2007 as applied to the above rejection have been fully considered and not been found persuasive to remove the above rejection. Applicant argues that the most recent amendment obviates the cited references, specifically by requiring that therapy commence at least 29 days post-transplantation. However, as discussed above, the

prior art provides clear motivation for switching patients from systemically active to topically active corticosteroids in order to avoid the systemic side effects of corticosteroid therapy. In many patients this switch would occur 29 days or more post-transplantation, giving rise to the claimed method. In fact, it would be particularly preferred to switch medications in patients who had been receiving systemically active corticosteroids for the longest period of time, as they would be expected to suffer the most from the side effects of this therapy.

Therefore the rejection is deemed proper and made **FINAL**.

Applicant's attention is further drawn to the reference Smith et al., which is made of record in this office action. Smith et al. discloses a study of the glucocorticoid receptor binding and transcriptional activation of a number of topically active glucocorticoids. (p. 957, left column, paragraph 3) Mometasone furoate, fluticasone propionate, triamcinolone acetonide, and budesonide are all disclosed as being topically active glucucoritcoids that bind to the glucocorticoid receptor and activate transcription. (P. 958, figures 1-3, p. 959, table 1) As all of these compounds are disclosed to be topically active and to activate the same receptor, one of ordinary skill in the art would recognize that mometasone furoate, fluticasone propionate, and triamcinolone acetonide can be substituted for budesonide in the above-mentioned references.

Summary

No claims are allowed in this application. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Eric Olson
Patent Examiner
AU 1623
11/20/07

Anna Jiang
11/21/07
Supervisory Patent Examiner
AU 1623